histidine tag motif; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the anti-angiogenic restin protein comprising at least one amino acid residue resulting from the linker polynucleotide, and wherein the protein additionally comprises a histidine tag motif;

thereby producing a biologically active anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof.

26. (Amended) The method of Claim 25 wherein the polynucleotide additionally encodes endostatin, angiostatin, or mutants, derivatives, fragments or fusion proteins thereof, or any combination thereof.

REMARKS

Claims 1-39 are currently pending in the application. Claims 1-4, 6, 8-9, 14-17, 22-23, 25-26, 36 and 38 are currently under examination. Claims 5, 7, 10-13, 18-21, 24, 27-35, 37 and 39 are withdrawn as being directed to a non-elected invention. Claims 36 and 38 are canceled. Claims 1, 8-9, 14, 17, 22-23 and 25-26 are amended. The amendments find support in the specification, claims and drawings as originally filed, and are made to reflect the election in the Restriction Requirement. No new matter is added by the amendments.

Objection to the Specification

The specification has been objected to because it contains an embedded hyperlink and/or other form of browser-executable code.

Applicant has deleted this code by amendment to the specification. Specifically, the paragraph at page 18, lines 16-22 has been replaced, and the hyperlink replaced with the statement that the BLAST programs are "available to the public on the world wide web at the web site of the National Center for Biotechnology Information (".ncbi"), National Library of Medicine (".nlm"), National Institutes of Health (".nih") of the United States government

(".gov")". Entry of the amendment is respectfully requested.

Claim Rejections Under 35 U.S.C. § 102(e)

Claims 1-4, 8-9, 14-16, 22 and 25 have been rejected under 35 U.S.C. § 102(e) as anticipated by Davidson (U.S. Pat. No. 6,057,122). The Examiner states that Davidson discloses a method for producing proteins from the kringle 5 regions of mammalian plasminogen, for purposes of treating angiogenesis. The kringle proteins are produced by transforming *P. pastoris* with an expression vector containing a nucleic acid encoding the kringle 5 protein.

In the Reply to the Restriction Requirement, Applicant elected the claims of Group V, directed to methods of producing restin protein. Applicant has therefore amended the claims to recite this subject matter.

In order to anticipate a claim, each and every element of the claim must be found in a single reference. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Davidson does not disclose methods of producing restin protein, and therefore does not anticipate the claims as amended. Applicant therefore respectfully requests that the rejection on this basis be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 6 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable in view of Davidson (U.S. Pat. No. 6,057,122). Claims 23, 26, 36 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable in view of either O'Reilly *et al.* (Int. App. WO 97/15666) or Hägg *et al.* (*Genomics* 45:31-41, 1977), in view of Davidson.

The Davidson Reference

Claims 6 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable in view of Davidson (U.S. Pat. No. 6,057,122). The Examiner states that while Davidson fails to disclose production of the kringle proteins at a concentration of 10-20 milligrams or more per liter of

culture fluid, it would have been obvious for one of ordinary skill to use the method of Davidson to produce "the product protein" at such a concentration.

The Davidson reference fails to render obvious Applicant's claims. The Manual of Patent Examining Procedure discusses obviousness at §§ 2142 and 2143, stating that

> To establish a prima facie case of obviousness, three basic criteria must be met. **First**, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. **Second**, there must be a reasonable expectation of success. **Finally**, the prior art reference (or references when combined) must teach or suggest all the claim limitations. **The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.** *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

(MPEP § 2142, emphasis added), and that

> The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references."

(MPEP § 2142, citing *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)).

Davidson (the '122 patent) teaches the production of Kringle 5 in *P. pastoris* with an expression vector that the Examiner believes is similar to the expression vectors described in the instant application, and further, that the Examiner believes that the culture conditions used by Davidson are similar to those used by Applicant. The Examiner thus believes that it would be *prima facie* obvious for one of skill in the art to make the protein as claimed in the instant claims 6 and 17.

Applicant respectfully disagrees. Davidson (the '122 patent) teaches a Kringle 5 peptide compound, methods of making Kringle 5 peptide and methods of using Kringle 5 peptide.

Kringle 5 peptide is a fragment of plasminogen.

Applicant claims a method of producing restin, a proteolyte fragment and part of the collagen type XV family. Kringle 5 peptide and restin are distinct proteins and the '122 patent neither teaches nor even remotely suggests the existence of restin, let alone a method of producing it in *P. pastoris*. Therefore the '122 patent does not make obvious the methods of claims 6 and 17 and reconsideration and withdrawal of the rejection is requested.

The O'Reilly and Hägg References

Claims 23, 26, 36 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable in view of either O'Reilly *et al.* (Int. App. WO 97/15666) or Hägg *et al.* (*Genomics* 45:31-41, 1977), in view of Davidson. The Examiner states that O'Reilly *et al.* teaches an inhibitor of cell proliferation that corresponds to the C-terminal fragment of collagen Type XVIII, and that Hägg *et al.* teaches "collagen type XV and discloses that the C-terminal regions of collagen type XVIII and XV are highly homologous and similar in their overall domain structure". The Examiner relies on Hägg *et al.* as stating that collagen types XV and XVIII are "highly homologous", and concludes that O'Reilly *et al.* therefore discloses restin, and that Applicant's claims to restin therefore include collagen XVIII. Applicant's disagree.

Claims 36 and 38 have been canceled. Claims 23 and 26, as amended, are drawn to methods of producing a fusion protein comprising restin and either angiostatin, endostatin or variants thereof. The rejection is based on the combination of three references, O'Reilly, Hägg and Davidson. However, it is axiomatic that if one of the cited references fall, then the combination falls. Applicant submits that none of the cited references either alone or in combination, teach the invention claimed in Claims 23 and 26.

O'Reilly *et al.* teaches endostatin, which is defined as an anti-angiogenic protein constituting the C-terminal domain of collagen type XVIII from mouse, and starting with the amino acid sequence "HTHQDFQPVLHLVALNTPLS" (the "HTH" sequence; SEQ ID NO:1 from O'Reilly *et al.*). Anti-angiogenicity is not the primary natural function of collagen type XVIII, and one of ordinary skill in the art would therefore not necessarily assume that anti-angiogenic properties of mouse collagen type XVIII (*i.e.*, endostatin) would necessarily be found

in human collagen type XV (*i.e.*, restin).

Furthermore, Applicant respectfully submits that O'Reilly *et al.* teaches away from the present invention. This reference discloses only a single sequence, an amino acid sequence of 20 residues (the HTH sequence). Nowhere in this reference is the actual sequence of endostatin provided, nor does the reference even refer the reader to a subsequence of a GenBank entry for collagen XVIII. The only definition of endostatin provided in O'Reilly *et al.* is that it is a protein having anti-angiogenic activity, a molecular weight of 18-20 kDa, is isolated and purified from the murine hemangioendothelioma EOMA cell line, and that the first 20 amino acids are provided as SEQ ID NO:1. In addition, a BLAST search (default parameters) using the HTH sequence produces no hits to collagen XV sequences (Exhibit A), and a BLAST alignment analysis between the 20-amino acid sequence of O'Reilly *et al.* and the protein sequence of restin shows no significant similarity (Exhibit B). One of ordinary skill, at the time the invention was made, would not have been able to use the reference of O'Reilly *et al.* to derive the usefulness of restin.

O'Reilly *et al.* states on page 14, line 25 to page 15, line 6 that:

> Alternatively, endothelial proliferation inhibiting proteins, or endostatins, of the present invention may be isolated from larger known proteins, such as human alpha 1 type XVIII collagen and mouse alpha 1 type XVIII collagen, proteins that share a common or similar N-terminal amino acid sequence. Examples of other potential endostatin source materials having similar N-terminal amino acid sequences include *Bos taurus* pregastric esterase, human alpha 1 type 15 collagen, NAD-dependent formate dehydrogenase (EC 1.2.1.2) derived from *Pseudomonas sp.*, s11459 hexon protein of bovine adenovirus type 3, CELF21D12 2 F21d12.3 *Caenorhabditis elegans* gene product, VAL1 TGMV AL1 protein derived from tomato golden mosaic virus, s01730 hexon protein derived from human adenovirus 12, *Saccharomyces cerevisiae*. For example, peptides closely related to endostatin may be derived from BOVMPE 1 pregastric esterase (BOS TAURUS) gene sequence corresponding to amino acids 502 to 521, and collagen alpha 1 type 15 from humans beginning at amino acid 316 ending at 335.

Applicant notes that a search of GenBank for pregastric esterase sequences from cow

revealed the three hits shown in Exhibit C, none of which showed any significant similarity when BLASTed against the HTH sequence. In fact, all three of these cow sequences are only 397 amino acids long, whereas O'Reilly *et al.* clearly states (at page 15, lines 4-5) that peptides closely related to endostatin may be derived from amino acids 502 to 521 of the pregastric esterase sequence. The reader is therefore directed to a portion of the molecule which does not exist.

O'Reilly *et al.* then specifically points to amino acids 316-335 of collagen type XV α1 from humans as a source of other endostatins, and the fact that amino acids 316-335 is 20 amino acids long would suggest to the person of skill in the art that these amino acids must match the HTH sequence in some way. However, a GenBank search of human collagen type XV sequences (Exhibit D), shows no sequences where the HTH sequence bears any resemblance to amino acids 316-335, as shown below:

O'Reilly *et al.* SEQ ID NO:1:	hthqdfqpvlhlvalntpls
XP_038785 amino acids 316-335:	kqgsgeilndtlegvhsvdg
P39059 amino acids 316-335:	kqgsgeilndtlegvhsvdg
NP_034058 amino acids 316-335:	qgsgeilndtlevhamdgdp
AAG27545 amino acids 316-335:	qgsgeilndtlevhamdgdp
A53317 amino acids 316-335:	kqgsgeilndtlegvhsvdg
NP_001846 amino acids 316-335:	kqgsgeilndtlegvhsvdg
BAA04762 amino acids 316-335:	kqgsgeilndtlegvhsvdg
AAC78500 amino acids 316-335:	kqgsgeilndtlegvhsvdg
AAC53387 amino acids 316-335:	qgsgeilndtlevhamdgdp
AAB23936	(only 41 amino acids long)
AAA58429 amino acids 316-335:	kqgsgeilndtlegvhsvdg

In summary, there is no GenBank entry for collagen XV in which amino acids 316-335 bear any resemblance to the sequence provided by O'Reilly *et al.*

BLAST analyses were also conducted between the HTH sequence from O'Reilly *et al.* and NAD-dependent formate dehydrogenase (Exhibit E), the hexon protein from bovine adenovirus type 3 (Exhibit F), the F21D12.3 *C. elegans* protein (Exhibit G), protein AL1 from tomato golden mosaic virus (Exhibit H), the hexon protein from human adenovirus 12 (Exhibit I). None of these sequences, when BLASTed against the HTH sequence, showed any significant similarity. Not only does the HTH sequence show no significant similarity to the restin protein (see Exhibit B), but, like the cow pregastric esterase sequence, the amino acids cited in the

reference appear to have nothing to do with the HTH sequence.

The passage cited on page 14 and 15 of O'Reilly *et al.* therefore appears to be completely erroneous, and teaches the person of skill in the art absolutely nothing about actually obtaining "other endostatins". Of the eight biomolecules suggested, not one bears any resemblance to the 20-amino acid long sequence provided in O'Reilly *et al.*. The person of skill in the art therefore cannot reasonably derive any endostatin equivalents at all from this supposed "disclosure". There is no reasonable expectation of success, and the only possible expectation of success comes in hindsight, using Applicant's disclosure as a roadmap. The rejection by the Examiner therefore represents impermissible hindsight reconstruction.

The Hägg *et al.* reference fails to supply the deficiencies of O'Reilly *et al.*. Hägg *et al.* is a study comparing the mouse and human collagen type XV chains, and comparisons to types XV and XVIII are made only in passing. Hägg *et al.* notes (on page 33) that the sequence homology between mouse collagen type XV and human collagen type XV is 84%. The homology between mouse collagen type XV and mouse collagen XVIII, however, is only 64% (page 33). Hägg *et al.* does not appear to provide any values regarding the comparison of mouse collagen type XVIII (endostatin) with human collagen type XV (restin), but a study of Fig. 4 (page 37) shows these two sequences to have 52.7% identity and 66.7% similarity in the C-terminal non-collagenous region only. When one compares the full length of the α chains of these two collagen types (see, *e.g.*, Exhibit I, which is a BLAST analysis of mouse collagen type XVIII (GenBank Accession No. P39061) and human collagen type XV (GenBank Accession No. P39059)), one finds that the actual sequence identity between these two proteins is only 39%, with a sequence homology of 48%.

As discussed above, the prior art reference (or references when combined) must teach or suggest all the claim limitations, and must provide a reasonable expectation of success, and the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

Hägg *et al.* provides no teaching, suggestion or motivation directing one of ordinary skill to look for anti-angiogenic properties in collagen XV, but merely states that collagens XV and XVIII have some homology. This reference does not suggest that anti-angiogenic activity, which

is a very unusual activity, and not an activity of the native mouse collagen XVIII molecule, might be found in human collagen XV. This reference simply states a fact (*i.e.*, the two molecules share some homology), but does not teach or suggest that the anti-angiogenic activity found in mouse collagen XVIII can also be found in human collagen XV. Hägg *et al.* therefore fails to provide the teaching or suggestion required to motivate one to look for anti-angiogenic activity in the collagen XV molecule. As stated above, such teaching or suggestion must come from the art itself, not Applicant's disclosure. Applicant respectfully submits that the "teaching" that would motivate one to look for anti-angiogenic proteins within collagen XV cannot be found in Hägg *et al.*, but in a hindsight reading of the present specification.

The art cited by the Examiner also fails to lay out to one of ordinary skill that there would be a reasonable expectation of success were one to search for anti-angiogenic peptides within collagen XV. It is well known that conservation of structure does not necessarily produce conservation of function, and conversely, it is also well known that molecules with very different structures can have similar functions. The "high homology" mentioned by Hägg *et al.* is in reference to the two molecules' overall structures and functions as *collagen* molecules, not as anti-angiogenic proteins, and any stated speculations regarding conserved function would be understood by one of ordinary skill to mean that the two molecules may share some functions as whole collagen molecules, not as proteolytically-produced molecules extracted from cell culture media (O'Reilly *et al.*, page 32, line 31 to page 33, line 6; page 44, lines 23-29).

The best that can be said is that, after reading in O'Reilly *et al.* that endostatin is from collagen XVIII, and learning from Hägg *et al.* that collagen XV has some homology to XVIII, is that one of ordinary skill in the art would find it obvious to try to look for anti-angiogenic properties within collagen XV. However, the Federal Circuit has long held that "obvious to try" does not constitute "obviousness." The court in *In re O'Farrell* (853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988)) made an excellent distinction between these two concepts. Judge Rich noted that "[a]ny invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?" (*Id.* at pages 1680-81). He went on to state that

> The admonition that 'obvious to try' is not the standard under §

> 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *[4 case cites omitted]*. In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.*, at 1681). The "motivation" provided by Hägg *et al.*'s statements of homology clearly falls into Judge Rich's second category. It is not at all clear that an activity that does not exist in an intact native molecule (collagen XVIII) would exist in another, homologous, intact native molecule (collagen XV), when those molecules are encoded by different genes on different chromosomes, expressed in different cells types and tissues, and have different functions. Davidson teaches only a general approach to making an anti-angiogenic protein. One of ordinary skill in the art might have been inspired to experiment, but nothing in the references suggested to combine their teachings to arrive at the claimed invention with a reasonable expectation of success.

The Federal Circuit has stated that "[i]t is impermissible . . . simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps . . . . The references themselves must provide some teaching whereby the applicant's combination would have been obvious." (*In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991)), and that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching[,] suggestion or incentive supporting the combination" (*In re Geiger*, 815 F.2d 686, 688, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987)).

> The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would

have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)).

MPEP § 2142. An unstated desire to find and produce additional anti-angiogenic proteins is not enough of a suggestion to render Applicant's claims obvious, and mere statements of sequence homology offer no reasonable expectation of successfully finding such proteins.

Applicant respectfully submits that the Examiner has engaged in impermissible hindsight reconstruction, using Applicant's invention as a roadmap to combine the references. None of the cited references, alone or in combination, teach or suggest the claimed invention. It is therefore requested that the rejection on this basis be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Rejections of Claims 1-4, 6, 8-9, 14-17, 22-23, 25-26, 36 and 38

Claims 1-4, 6, 8-9, 14-17, 22-23, 25-26, 36 and 38 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 36 and 38 have been canceled.

The Examiner states that the claims are genus claims that encompass a wide array of molecules, that the specification does not disclose any variants or modifications, teachings as to how the structures of these sequences relate to their function, the complete structure of a representative number of species, or partial structure and relevant identifying characteristics. The Examiner then states that "[t]he specification is not enabled for any mutant, fragment, fusion protein or variant of an anti-angiogenic protein and specifically restin. A multitude of mutants and variants may be gencrated that may or may not have the desired activity. The specification does not provide any guidance on which fragments may retain the anti-angiogenic activity or what motifs are required for said activity." The Examiner relies on *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991).

Written Description Standard

As stated by the MPEP at § 2163.02, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed", that is, whether or not one of ordinary skill in the art would recognize that Applicant had invented the subject matter claimed. The MPEP states that

> the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement.

(at § 2163.02) and that "[t]he examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." (at § 2163.04).

As stated in the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1, 'Written Description' Requirement" (*Federal Register*, Vol. 66, No. 4, January 5, 2001) (hereinafter, the *Guidelines*), "the 'essential goal' of the description of the invention requirement is to clearly convey the information **that an applicant has invented the subject matter which is claimed**." (at 1104, quoting *In re Barker*, 599 F.2d 588, 592 n. 4, 194 U.S.P.Q. 470, 473 n. 4 (C.C.P.A. 1977), emphasis added). The *Guidelines* also outline the procedure for determining whether or not a specification is in compliance with 35 U.S.C. § 112, first paragraph:

> Office personnel should adhere to the following procedures when reviewing patent applications for compliance with the written description requirement of 35 U.S.C. 112, ¶ 1. The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. **There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed**; [citing *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976)] however, with respect to

> newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims. [citing MPEP §§ 714.02 and 2163.06] **Consequently, rejection of an original claim for lack of written description should be rare.** The inquiry into whether the description requirement is met is a question of fact that must be determined on a case-by-case basis. [citing *In re Smith*, 458 F.2d 1389, 1395, 173 U.S.P.Q. 679, 683 (C.C.P.A. 1972)]

(at 1105, emphasis added).

The Examiner states that the claims are genus claims that encompass a wide array of molecules, and that the specification does not disclose any variants or modifications, or disclose any teachings as to how the structures of these sequences relate to their function. However, Applicant has disclosed apomigren (see, *e.g.*, page 12, lines 24-27; page 21, lines 11-24; page 59, lines 5-6), which is a fragment of full-length restin comprising the last approximately 85 amino acid residues of restin itself, from about amino acid 97 to about amino acid 181. Applicant has also provided methods for cloning and assaying apomigren, and other fragments of full-length restin can be similarly cloned and assayed for anti-angiogenic activity.

The restin protein is represented in SEQ ID NO:20. Therefore, the "structure" of restin is the sequence as represented in SEQ ID NO:20, and fragments of restin will be fragments of SEQ ID NO:20. Full-length restin is in turn a subsequence of full-length collagen XV. Collagen XV is not known to have any anti-angiogenic properties, and so it is not clear that any further structural characteristics are required for restin's anti-angiogenic activity, beyond its sequence.

Comment 9 of the *Guidelines* also specifically rejects the idea that claims must always be limited to the precise sequence disclosed, and clearly states that a DNA sequence **IS** the complete chemical structure of that sequence:

> (9) *Comment*: One comment stated that the written description of a claimed DNA should be required to include the complete sequence of the DNA and claims should be limited to the DNA sequence disclosed. *Response*: **Describing the complete chemical structure, *i.e.*, the DNA sequence, of a claimed DNA is one method of satisfying the written description requirement, but it is not the only method.** See *Eli Lilly*, 119 F.3d at 1566, 43

> USPQ2d at 1404 ("An adequate written description of a DNA * * * requires a precise definition, *such as* by structure, formula, chemical name, or physical properties." (emphasis added, internal quote omitted)). Therefore, there is no basis for a *per se* rule requiring disclosure of complete DNA sequences or limiting DNA claims to only the sequence disclosed.

(at 1101, emphasis added).

Furthermore, the specification does disclose the correlation and relationship between the structure (*i.e.*, the sequence) of these proteins and their functional activities. Apomigren is a subsequence of full-length restin, and apomigren possesses the anti-angiogenic activity of full-length restin. One of ordinary skill would therefore understand that the region responsible for anti-angiogenic activity is somewhere within the region making up the apomigren sequence. Therefore, contrary to the Examiner's contentions, the specification does indeed describe the very correlation and relationship that the Examiner requires, and one of ordinary skill in the art therefore would envisage the genus of restin fragments and variant other than the precise species disclosed.

The complete structure and function of each amino acid and fragments thereof encompassed by these claims is fully in the possession of those of ordinary skill in the art, because the specification contains all of the information necessary to create any potentially useful fragment of SEQ ID NO:20, and methods to assay each for the activity required to bring the fragment within the scope of the claims. Thus, it is clear that Applicant has complied with the written description requirement by both (1) having reasonably conveyed to those of ordinary skill in the art that he had invented the claimed subject matter, *i.e.*, that Applicant had possession of the claimed subject matter, and (2) having placed the subject matter of the claims within the possession of the ordinarily skilled artisan.

In addition, the specification contains numerous working examples demonstrating the correlation and relationship between the sequence (*i.e.*, the structure) and functional activities of the claimed proteins, as well as methods of assaying additional proteins for such activities. Applicant has therefore provided teachings which guide the ordinarily skilled artisan in assessing the functional activities of any additional fragments that such an artisan may wish to make.

Furthermore, there is no requirement that an applicant show one of ordinary skill in the art how to do that which is well known in the relevant art. As stated in the Manual of Patent Examining Procedure at § 2164.01, "[a] patent need not teach, and preferably omits, what is well known in the art." (citing *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinen-fabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984)).

Many compounds are routinely altered in the course of practicing the pharmaceutical arts, *e.g.*, proteins and peptides are "PEGylated" to increase their circulatory half-life, amino acids residues are added to increase recombinant production, proteins are chemically modified to allow addition of other molecules, etc. To require Applicant to teach all such methods to protect the claimed subject matter would be requiring Applicant to teach what is well known, and would give copyists free rein to avoid infringement by making insignificant changes in the anti-angiogenic proteins and peptides. Methods for modifying known sequences, *e.g.*, methods of truncating sequences, making deletion mutants of known sequences, site-directed mutagenesis, etc., are also common in the art, and are well-known to those of ordinary skill. For example, a person of ordinary skill can prepare a portion of SEQ ID NO:2 wherein the portion encodes an anti-angiogenic peptide, by simply deleting a few N-terminal or C-terminal amino acids of SEQ ID NO:2. Thus, the claimed invention prevents potential infringers from deleting a few amino acids in an attempt to avoid the scope of Applicant's claims. Because methods for making truncated sequences, deletion mutants, chemical modifications, etc. are routine, and because Applicant has taught how to analyze such sequences for the anti-angiogenic activity recited in the claims, Applicant respectfully submits that disclosure has been provided for the full scope of the claimed invention.

The Examiner has also stated that the specification does not disclose the complete structure of a representative number of species, or partial structure and relevant identifying characteristics.

Applicant knows of no requirement to disclose the complete structure of a representative number of species. The *Guidelines* state that

> [t]he written description requirement for a claimed genus **may be** satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a), above), reduction to drawings (see (1)(b), above), or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above).

(at 1106, third column, citing *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997)). That is, a representative number of species may be described by

(1) actual reduction to practice,

(2) reduction to drawings, OR

(3) by disclosure of relevant, identifying characteristics, *i.e.*,

  (a) structure or other physical and/or chemical properties,

  (b) by functional characteristics coupled with a known or disclosed correlation between function and structure, OR

  (c) by a combination of such identifying characteristics.

The *Guidelines* therefore provide a number of different ways in which one can describe a representative number of species.

As discussed above, the instant specification in fact describes precisely such a relationship, that is, the relationship between the structure, that is, the sequence of the restin protein, and its disclosed function (*i.e.*, anti-angiogenic activity). Applicant has also shown that this function can be further localized to a particular region within SEQ ID NO:20, that is, the region making up the apomigren sequence. One of ordinary skill in the art would therefore understand that Applicant has disclosed the correlation between this function and a specific structure, that is, the protein sequence.

Furthermore, Applicant has also disclosed a representative number of species by actual reduction to practice, and by reduction to drawings (*i.e.*, by disclosing the sequence). Applicant has therefore properly described the genus of restin subsequences by providing the overall

sequence, localization of the active region, and methods for assaying additional fragments, variant, etc. for this same activity.

The Examiner also believes that "[a] multitude of mutants and variants may be generated that may or may not have the desired activity", and that "[t]he specification does not provide any guidance on which fragments may retain the anti-angiogenic activity or what motifs are required for said activity".

As discussed above, there is no evidence or indication that any "motifs" are required for anti-angiogenic activity, beyond the basic protein sequence of the restin molecule. In addition, there is no requirement that every possible mutant or variant have the desired activity. The Federal Circuit has held that claims may encompass some inoperative species, so long as the number of inoperative species does not become significant and force one of ordinary skill into undue experimentation in order to practice the invention, and that "[i]t is not a function of the claims to specifically exclude possible inoperative substances." (*Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984)). "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue,' not 'experimentation' ' " (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

The Examiner refers Applicant to *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). This case was an interference between two parties regarding claims to DNA sequences encoding erythropoietin (EPO). Amgen had claimed all DNAs encoding analogs of the erythropoietin protein that were biologically active. The court noted that substitution of a single amino acid resulted in over 3600 possible DNA analogs, and over one million possible DNA analogs if only three amino acids were substituted. The Court concluded that "the number of claimed DNA encoding sequences that can produce an EPO-like product is potentially enormous" (*Id.* at 1026). Applicant believes that it is worth noting that the claim at issue in that case recited a "purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence *sufficiently duplicative of that of erythropoietin* to allow possession of the biological property . . . ." In contrast, Applicant is

not claiming nucleic acid sequences, but methods of producing anti-angiogenic restin protein. Applicant respectfully submits that unlike the claims in *Amgen*, Applicant has supplied sufficient structure (in the form of protein sequences) to reasonably convey to one of ordinary skill in the art that Applicant was in possession of the invention at the time the application was filed.

Because Applicant has provided the structure (*i.e.*, the sequence) of the full-length restin and apomigren (a fragment of restin), and methods of assaying same for anti-angiogenic activity, Applicant submits that support has been provided for the full scope of the claims, and respectfully requests that the rejection on this basis be reconsidered and withdrawn.

Rejection of Claims 3, 14-17, 22-23, 25-26, 36 and 38

Claims 3, 14-17, 22-23, 25-26, 36 and 38 are also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner believes that a biological deposit is necessary for Applicant to satisfy the written description requirement.

Claims 36 and 38 have been canceled.

Applicant notes that the court in *Amgen* addressed the subject of deposit of biological materials, and held that "[i]f the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. *See Feldman v. Aunstrup*, 517 F.2d 1351, 1354, 186 USPQ 108, 111 (CCPA 1975), ("No problem exists when the microorganisms used are known and readily available to the public."), *cert. denied*, 424 U.S. 912 [188 USPQ 720] (1976)." (*Id.* at 1025). For instance, the Board of Patent Appeals and Interferences has held that a description of the precise geographic location of marine tunicates, as a biological material, used in a claimed invention was adequate to satisfy the requirements of 35 U.S.C. § 112, first paragraph (MPEP § 2404.01).

The plasmids and vectors described in the specification were all assembled from commercially-available starting materials (*e.g.*, the Pichia expression kit, available from Invitrogen (see, *e.g.*, page 57, lines 5-7) using methods (*e.g.*, PCR cloning) well-known to those in the field. See, *e.g.*, Example 25 (pages 56-59), Fig. 24, and elsewhere in the specification.

One of ordinary skill in the art can therefore construct plasmids satisfying the limitations of the claims from known and readily-available materials, without undue experimentation. A biological deposit is not required for one of ordinary skill in the art to practice the invention, and Applicant respectfully requests that the rejection on this basis be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-6, 6, 8-9, 14-17, 22-23, 25-26, 36 and 38 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner believes that the claims are indefinite because "they claim . . . restin, and derivatives thereof", and that "derived" is a term that is "non-specific and relative in nature for which Applicant provides no definition", that it is "impossible to determine what and how many derivations comprise the invention", and the "nature and number of the derivations . . . are not established".

Claims 36 and 38 have been canceled.

Applicant wishes to point out that the claims recite methods of making restin protein, or biologically active mutants, fragments, derivatives or fusion proteins thereof. Applicant does not actually claim these molecules, but rather, methods of making same.

Applicant has discussed and defined "derivatives" of the proteins throughout the specification, *e.g.*, at page 4, lines 2-3, page 19, lines 7-11, page 22, lines 19-23, page 23, lines 1-17, etc. The term is therefore defined.

Applicant submits that one of ordinary skill in the art would understand what is meant by a "chemical derivative" of a protein, and therefore respectfully requests that the rejection on this basis be reconsidered and withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 18, lines 16 through 22 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Identity is often measured using sequence analysis software *e.g.*, BLASTN or BLASTP (available to the public on the world wide web at the web site of the National Center for Biotechnology Information (".ncbi"), National Library of Medicine (".nlm"), National Institutes of Health (".nih") of the United States government (".gov") [at http://www.ncbi.nlm.nih.gov/BLAST/]). The default parameters for comparing two sequences (*e.g.*, "Blast"-ing two sequences against each other[, http://www.ncbi.nlm.nih.gov/gorf/bl2.html]) by BLASTN (for nucleotide sequences) are reward for match = 1, penalty for mismatch = -2, open gap = 5, extension gap = 2. When using BLASTP for protein sequences, the default parameters are reward for match = 0, penalty for mismatch = 0, open gap = 11, and extension gap = 1.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method of producing a biologically active anti-angiogenic restin protein, or a biologically active mutant, fragment, derivative or fusion protein thereof, comprising:

(a) inserting an isolated polynucleotide comprising a polynucleotide sequence encoding an anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof, into a yeast expression vector, wherein the vector contains a multiple cloning site; and

(b) transforming an appropriate yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the anti-angiogenic restin protein, or the mutant, derivative, fragment or fusion protein thereof;[,]

thereby producing a biologically active anti-angiogenic restin protein, or mutant, derivative, fragment or fusion protein thereof.

6. (Amended) The method of Claim 1 wherein the restin protein, mutant, derivative, fragment or fusion protein is produced at a concentration of 10-20 milligrams or more per liter of culture fluid.

8. (Amended) The method of Claim 1 wherein the isolated polynucleotide of step (a) additionally comprises a polynucleotide linker and the anti-angiogenic restin protein, mutant, derivative, fragment or fusion protein thereof produced in step (b) additionally comprises at least one amino acid residue resulting from the [linker] polynucleotide linker.

9. (Amended) The method of Claim 8 wherein the anti-angiogenic restin protein, mutant, derivative, fragment or fusion protein produced comprises two additional amino-terminus amino acid residues.

14. (Amended) The method of Claim 1 wherein the vector of step (a) comprises a pPICzαA plasmid wherein the plasmid contains a multiple cloning site, said cloning site comprising a His.Tag motif and wherein the anti-angiogenic restin protein, mutant, derivative, fragment or fusion protein thereof produced in step (b) comprises a histidine tag motif.

17. (Amended) The method of Claim 14 wherein the restin protein, mutant, derivative, fragment or fusion protein is produced at a concentration of 10-20 milligrams or more per liter of culture fluid.

22. (Amended) A method of producing a biologically active anti-angiogenic restin protein, or a biologically active mutant, fragment, derivative or fusion protein thereof, comprising:

(a) inserting an isolated polynucleotide comprising a polynucleotide sequence encoding an anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the anti-angiogenic restin protein comprising at least one amino acid residue resulting from the linker polynucleotide;[,]

thereby producing a biologically active anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof.

23. (Amended) The method of Claim 22 wherein the polynucleotide additionally encodes angiostatin, endostatin, [restin] or mutants, derivatives, fragments or fusion proteins thereof, or any combination thereof.

25. (Amended) A method of producing a biologically active anti-angiogenic restin protein,

or a biologically active mutant, fragment, derivative or fusion protein thereof, comprising:

(a) inserting an isolated polynucleotide comprising a polynucleotide sequence encoding an anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site and wherein the cloning site additionally comprises a histidine tag motif; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the anti-angiogenic restin protein comprising at least one amino acid residue resulting from the linker polynucleotide, and wherein the protein additionally comprises a histidine tag motif;[,]

thereby producing a biologically active anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof.

26. (Amended) The method of Claim 25 wherein the polynucleotide additionally encodes endostatin, angiostatin [or restin], or mutants, derivatives, fragments or fusion proteins thereof, or any combination thereof.